REMARKS

The Amendments

Claims 11 and 56 have been amended to cancel non-elected subject matter, particularly "a γ subunit." Claims 12 and 57 are cancelled as redundant in view of the amendment to claims 11 and 56.

Claims 11, 14, 15, 16, 17, 18, 19, 24, and 56 have been amended to remove references to bioluminescence resonance energy transfer (BRET) and now recite only fluorescence resonance energy transfer (FRET). New claims 77-93 have been added. The new claims are specifically directed to the BRET subject matter removed from the previous claims.

The amendments introduce no new matter.

The Objection to the Specification

The title of the invention was objected to as not descriptive. The title of the invention has been amended to recite "Heterotrimeric G-Protein."

Applicants respectfully request withdrawal of the objection.

The Objections to the Claims

Claims 11 and 56 are objected to as containing informalities, specifically recitation of non-elected subject matter. The claims have been amended to delete the recitation of the γ subunit of G protein.

Applicants respectfully request withdrawal of the objection.

The Rejection of Claims 11, 13-25, and 56 Under 35 U.S.C. § 112, first paragraph

Claims 11, 13-25, and 56 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled for the full scope of the claims. Applicants have amended claims 11, 13-25, and 56 to remove the part of the claim (BRET) the Office Action contends is not enabled. Applicant has added new claims 77-93 reciting the subject matter removed from claims 11, 13-25 and 56. Applicants respectfully traverse the rejection as it would be applied to claims 77-93.

Section 112 of 35 U.S.C. states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention." The courts have interpreted this to mean that any experimentation that may be needed to practice the claimed invention by the skilled artisan must not be undue or unreasonable. "The key word is 'undue', not 'experimentation.'" *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d (BNA) 1400, 1404 (Fed. Cir. 1988). To satisfy 35 U.S.C. § 112, first paragraph, "the scope of the claims must bear *reasonable correlation* to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (C.C.P.A. 1970) (emphasis added). The teachings of the present specification meet this standard.

While acknowledging the enablement of the present specification for subject matter directed to fluorescence resonance energy transfer (FRET) the Office Action asserts that undue experimentation would be required to make G-protein fusions that would be capable of bioluminescence resonance energy transfer (BRET). The Office Action asserts that the specification does not provide "any details on which luminescent protein to use and how to

attach a luminescent protein with α or β subunits of G-protein." Office Action, page 4, lines 12-13. Applicants respectfully traverse.

The Office Action asserts that the specification does not enable a hetrotrimeric G protein capable of bioluminescence resonance energy transfer (BRET). Office Action, page 4, lines 7-12. The Office Action supports this assessment with the following:

- The "amount of guidance or direction provided by [the] specification...is very small and would require a large amount of experimentation..." Office Action, page 4, lines 14-19.
- "There are no working examples directed to BRET..." Office Action, page 4, lines 20-21.
- "[BRET] would require an optimization of distance between the donor and acceptor bioluminescent subunits of G-protein." Office Action, page 5, lines 9-11.
- "The state of the art with regard to BRET is evolving." Office Action, page 5, line 3.

The Office Action first asserts that a large amount of experimentation is required because Pfleger *et. al.* reports that the BRET signal is dependant upon the spectral properties, ratio distance and relative orientation of the donor and acceptor molecules as well as the strength and stability of the protein of interest. Office Action, page 4, lines 14-19. The scientific literature, however, teaches that FRET signal depends on the same factors. "FRET efficiency depends on spectral overlap, the relative orientation and the distance between the donor and acceptor fluorophores." Xu *et al.*, *Proc. Natl. Acad. Sci. USA 96*, 151-156, 151 1999. Appendix I. In

fact, the scientific literature teaches that the only difference between BRET and FRET is that, "In BRET, the donor flourophore of the FRET technique is replaced by a luciferase." *Id.* Beyond this one difference, the two techniques are considered interchangeable, as Xu *et al.* explain: "In the presence of a substrate, bioluminescence from luciferase excites the acceptor flurophore through the same Förster transfer mechanism described above [referring to FRET]." *Id.* Emphasis added. Further, Xu *et. al.* indicate that the techniques of BRET and FRET are interchangeable by referring to them collectively as "FRET/BRET." *Id.* at 153. Thus, the prior art recognized the extensive similarities between the two procedures. A practitioner able to utilize FRET would be able to utilize BRET without undue experimentation.

The Office Action asserts that there are no working examples directed to BRET and therefore one of skill in the art could not easily translate FRET into BRET without undue experimentation. Office Action, page 4, lines 20-21. The specification, however, does contain sufficient guidance to meet the legal standard for enablement.

First, a specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art would be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). Examples of BRET are not necessary so long as the specification adequately describes to one of skill in the art how to practice BRET without undue experimentation.

Second, a considerable amount of experimentation is acceptable under the legal standard. "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the

claimed invention." *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F. 3d 1342, 1360, 47 U.S.P.Q.2d (BNA) 1705, 1719 (Fed. Cir. 1998) (Emphasis added). Thus, if either (a) the type of experimentation required to practice BRET is routine, or (b) a reasonable amount of guidance is provided on how to practice BRET, then the use of BRET in the instant claims is enabled.

Both of the *Johns Hopkins* alternatives are satisfied. The type of experimentation is merely routine because the use of BRET was known in the prior art. One skilled in the art at the time of filing would have had knowledge of a variety of luminescent proteins and how to attach luminescent proteins to other polypeptides. Xu *et. al.* teach the use of *Renilla* luciferase and enhanced yellow fluorescent protein to measure interactions between circadian proteins in cyanobacteria. *Proc. Natl. Acad. Sci. USA 96*, 151-156, 1999. Angers *et. al.* teach the use of *Renilla* luciferase and green fluorescent protein to measure β2-adrenergic receptor dimerization in living cells. *Proc. Natl. Acad. Sci. USA*, *97*, 3684-3689, 2000. Appendix II. One skilled in the art would need only choose a bioluminescent protein and then follow the methodologies described in these references to practice BRET. Moreover, BRET was known to be highly similar to FRET, and the Patent Office has affirmed that FRET could be used without undue experimentation. Office Action, page 3, lines 2-7. Therefore one of skill in the art would find the use of BRET to be routine.

In addition, the specification provides practitioners with a reasonable amount of guidance to perform BRET with a G-protein. The specification teaches the use of yellow fluorescent protein and green fluorescent protein in FRET. "Two preferred fluorescent amino acid sequences are cyan fluorescent protein and yellow fluorescent protein. When maintained within a distance of about 10-100 angstroms these two proteins are capable of FRET." Page 9, lines 3-5. The specification teaches these same fluorescent moieties can be used with BRET if a light-

emitting luciferase moiety is used. "In addition, the closely related technique of bioluminescence energy transfer (BRET) can be used. The α- or βγ- subunits can comprise a light-emitting luciferase protein moiety that can excite a fluorescent protein moiety on the complementary subunit." Page 9, lines 15-18. The specification enables the use of FRET and teaches what specific modifications of FRET are necessary to practice BRET. This provides more than a reasonable amount of guidance to one skilled in the art.

The Office Action also asserts that BRET is unpredictable because bioluminescence would require optimization of distance between the donor and acceptor moieties. Office Action, page 5, lines 9-11. Optimization is merely routine experimentation that does not offend the enablement standard. "Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 858 F. 2d 731, 736, 8 U.S.P.Q.2d (BNA) 1400, 1404 (Fed. Cir. 1988). In addition, the method for optimization of distance between donor and acceptor luminescence proteins for BRET would not be unknown or unpredictable to one skilled in the art, as the Applicants taught how to optimize distance for fluorescent proteins in the similar FRET procedure. Page 11, lines 1-16.

The Office Action further asserts that BRET is not enabled because the state of the art with regard to BRET is evolving. Office Action, page 5, line 3. The Office Action cites a variety of post-filing date articles describing the use of BRET to study protein-protein interactions. Office Action, page 5, line 5. The standard of enablement does not involve a determination of whether the state of the art is currently evolving. Rather the standard of enablement requires a determination of whether the experimentation necessary to practice the invention is undue. See *In re Wands*, 858 F. 2d 731, 736-37, 8 U.S.P.Q.2d (BNA) 1400, 1404 (Fed. Cir. 1988).

The specification meets the enablement standard because one of skill in the art would have known that BRET is very similar to FRET. As detailed above, both the specification and the prior art taught that these techniques were very similar. Later, post-filing date publications support the specification's teaching of similarity between FRET and BRET. For example, in one recent paper the same expression vector system was used for both BRET and FRET. The only difference between the two sets of expression constructs was a bioluminescent moiety (luciferase) in BRET constructs and a fluorescent moiety (enhanced yellow fluorescent protein) in FRET constructs. Canals *et. al., J. Biol. Chem. (278)47*: 46741-46749 (2003). Appendix III. Recent reviews in the field also discuss the similarities between FRET and BRET:

> "FRET and BRET technologies are based on the nonradiative transfer of energy between donor and acceptor molecules via the Förster Mechanism, and primarily depend on (1) an overlap between the emission and excitation spectra of the donor an acceptor molecules, respectively; and (2) the close proximity of the donor and acceptor entities (<100 Å). In the case of FRET, both the donor and acceptor are fluorescent molecules, whereas in BRET, the bioluminescent molecule acts as the energy donor."

Eidne *et al., Trends Pharmacol Sci. (23)8*: 351-354 (2002). Appendix IV.

> "Resonance energy transfer approaches are based on the nonradiative transfer of energy between the electromagnetic dipoles of an energy donor and acceptor. In the case of fluorescence resonance energy transfer (FRET), both the donor and acceptor are fluorescent molecules, whereas for bioluminescence resonance energy transfer (BRET), the fluorescent donor moiety is replaced with the bioluminescent catalytic activity of an enzyme. Prerequisites for these processes are: (a) the existence of an overlap between the emission and excitation specta of the donor and acceptor molecules and (b) that the donor and acceptor be in close molecular proximity, typically <100 Å. The critical dependence on the molecular nearness between donor and acceptors for energy transfer (the efficiency of transfer decreases with the 6^{th} power of the distance) makes BRET and FRET systems of choice to monitor protein-protein interactions in living cells."

Angers *et al., Annu. Rev. Pharmacol. Toxicol. 42*, 409-435 (2002). Appendix V.

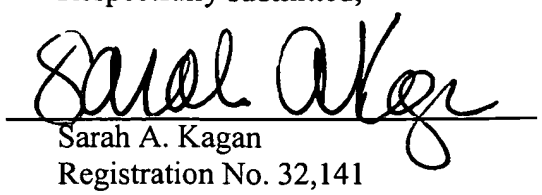
Thus, those of skill in the art continue to believe that BRET and FRET are highly similar.

One of skill in the art at the time the application was filed would have recognized that BRET is but a minor variation of FRET. The state of the art and the specification itself teach sufficient information for one skilled in the art who can practice FRET to also be able to practice BRET without recourse to undue experimentation.

The Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

Date: September 1, 2004

By: 

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